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JCIMCR OPEN ACCESS Journal of Clinical Images and Medical Case Reports

ISSN 2766-7820

Review Article

Open Access, Volume 2

Therapeutic approaches towards COVID-19: A critical insight

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Received: Jun 02, 2021

Accepted: Jul 12, 2021

Published: Jul 16, 2021

Archived: www.jcimcr.org

Abstract

Coronavirus disease 2019 (COVID-19) has been taking a heavy toll worldwide. Since its outcome, different therapeutic strategies have been formulated against COVID-19. Unfortunately, none of them alone or in combination has come out successful against this pandemic. Current review discusses the measures applied so far against COVID-19 and suggests future aspects for the betterment of the humankind.

Keywords: Anti-viral drugs; COVID-19; Plasma therapy; SARS-CoV-2; Vaccination.

Introduction

Since its inception in December 2019, coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory distress syndrome corona virus 2 (SARS-CoV-2) has remained a threat of every moment to every human of the globe. Medical scientists, researchers, health-care providers, policymakers and statesmen have tried their best and formulated multiple strategies to hold this pandemic on. Almost all the endeavors have ended in vain and new variant of the virus is posing much threat and death toll is skyrocketing. Medical and pharmacological interventions towards SARS-CoV-2 had focused mainly on treating the patients with drugs that could alleviate the COVID-19 symptoms, reduce the duration of stay of the hospitalized patients, application of different drugs already available to related symptoms and pathophysiology, preclinical and clinical trial of some old and new drugs for the COVID-19 patients, vaccine production followed by clinical trial and application to the public. Amidst numerous attempts undertaken, no one alone or in combination has come out with successful outcome so far. Sometimes, one or more drug has shown some positive signal for some time, but later, has been proven unsuccessful. Still, some of those have been suggested while others are prohibited. In a word, we are still in need of an efficacious drug to combat COVID-19. This article critically reviews strategies to withstand the SARS-CoV-2 with the old and novel therapeutic approaches for the sake of a COVID-free world.

Antiviral Therapy

Anti-viral therapy including drugs that inhibit entry of SARS-CoV-2 in host cell through disrupting binding of the virus with the host cell receptor, such as angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane serine protease 2 (TMPRSS2) or alters viral membrane fusion and endocytosis or the activity of the SARS-CoV-2 3-chymotrypsin-like protease (3CLpro), seem promising [1]. Besides, viral replication is an early event in COVID-19 pathogenesis and withstanding of viral multiplication is a serious concern of COVID-19 pathogenesis. Thus, inhibition of the SARS-CoV-2 RNA-dependent RNA polymerase comes out as a promising treatment stratagem for COVID-19 mitigation. In this context, anti-viral medications have received momentum in COVID-19 therapeutics. Anti-viral therapeutics would save the COVID-19 sufferers from severe hyper inflammatory state and "Cytokine Storm" *apriori.*

Drugs used to block viral entry into host cell

Camostat/Nafamostat: Synthetic protease inhibitors like camostat mesilate, gabexate mesilate and nafamostat mesilate have been found effective in reducing viral entry into host cell lines [2,3].

Umifenovir: Umifenovir alters viral dependent membrane fusion through impaired membrane phospholipid and thus prevents viral entry [2,3].

Blockage of viral proteases

Viral proteases mediate the proteolytic cleavage and release of functional polypeptides from the polyproteins during SARS-CoV-2 replication [4,5]. Functional polypeptides form the replicase–transcriptase complex that produces the SARS-CoV-2 RNA [4,5]. Translation of RNA into structural proteins and replicated genomic RNA give rise to novel infectious SARS-CoV-2 that is released from the host cell [4,5]. 3C-like protease (3CLpro) is the main protease (Mpro) in SARS-CoV-2 that cleaves the polyprotein and is an important target for blockage by the anti-viral drugs so that new infectious virus particles cannot be released [4,5]. Combination of lopinavir and ritonavir has been found effective in blocking the SARS-CoV-2 protease *in vitro* while monotherapy of ritonavir and darunavir had shown no considerable effect [6].

Viral RNA replicase inhibitor

Different nucleoside/nucleotide analogs have been used as SARS-CoV-2 replicase inhibitors. These structural analogs compete with endogenous nucleosides during the elongation phase and disrupt viral replication. They also mediate chain termination and abolishment of RNA synthesis and thus diminish novel viral particle production.

Remdisivir: Remdesivir (GS-5734), a prodrug of a monophosphoramidate nucleoside, passes the cell membrane easily and delivers its active metabolite efficiently [7]. In target cells, remdesivir monophosphate (RDV-MP) is rapidly converted into its active triphosphate form (RDV-TP) that acts as substrate for the viral replicase (RdRp) where it competes with endogenous (ATP) during elongation of RNA strands [8]. RDV-TP ensues delayed chain termination and synthesis arrest. Remdesivir (GS-5734) is an inhibitor of the viral RNA-dependent RNA polymerase that have been reported having *in vitro* inhibitory activity against SARS-CoV-1, SARS-CoV-2 and the Middle East respiratory syndrome (MERS-CoV) [9,10]. In 22nd October 2020, the food and drug administration (FDA) of the USA approved remdesivir, first produced by Gilead Sciences under the brand Veklury, for treating hospitalized COVID-19 patients aged over 12 years and weighing more than 88 pounds [9,10]. Remdesivir is capable of getting inserted into SARS-CoV-2 genome and disrupt virus's replication and multiplication [9,10]. Remdesivir had been reported speeding up COVID-19 recovery time from 15 to 11 days [9,10]. Though previously FDA recommended the usage of remdesivir only for critical patients, recently, FDA suggests its usage for all types of COVID-19 patients [9,10]. Originally, remdesivir had been regarded as an anti-viral agent against Ebola and Hepatitis C virus [9,10]. Based on some confounding results, some schools of thought opt against usage of remdesivir in COVID-19 cases. Even, WHO reported little or no benefit of remdesivir in COVID-19 patients [9,10]. However, neither usage nor price of remdesivir has slowed down. Excessive cost of remdesivir (five-day course worth 3,120 USD) keeps it beyond the means of the poor patients of the developing and underdeveloped nations.

Combination therapy

As remdesivir alone could not achieve the goal in withstanding COVID-19 progression, combined usage of it with other drugs stormed the COVID-19 researchers' brain.

Dexamethasone: COVID-19 patients at severe stage undergoe systemic inflammatory responses that causes multi-organ dysfunction [11,12]. Utilization of anti-inflammatory agents especially corticosteroids might dampen hyperinflammatory state [11,12]. On the other hand, corticosteroids in absence of anti-viral agents have been linked with reduced virus clearance or worsening virus-induced respiratory complications [13-16]. Thus, inclusion of anti-inflammatory agent dexamethasone with anti-viral drug remdesivir seemed apt in COVID-19 treatment [17]. This combined therapy reduced the necessity of ventilation in severe COVID-19 patients to some extent (rate ratio 0.82) [17]. However, data concerning the safety and efficacy of this combination therapy is not ample yet.

Baricitinib plus remdesivir: Corticosteroids could not be administered to some COVID-19 patients due to contraindication and in this context, the FDA approved the emergency use authorization (EUA) for baricitinib (a Janus kinase inhibitor) along with remdesivir in hospitalized children over 2 years and older patients necessitating ventilation [14-17]. This combination also reduced the dependency on mechanical ventilation [14-17]. However, combined therapy of the triad "Remdesivir-dexamethasone-baricitinib" awaits application.

Dexamethasone plus Tocilizumab: Dexamethasone-tocilizumab combination has not been reported providing beneficial effect to the COVID-19 patients [18-22].

Favipiravir: Favipiravir (T-705) is a pyrazine derivate that competitively inhibits the RdRp of SARS-CoV-2 [23]. Its active triphosphate form functions as a nucleotide analog that competes with ATP and GTP and affects RNA chain elongation [23]. Additionally, it is capable of causing point mutation in viral genome and thus lethal mutagenesis in viral life cycle [23]. Though cell

based studies indicated lower activity of favipiravir, its combination with liponavir/ritonavir improved hospitalized COVID-19 patients remarkably along with significant viral clearance [24].

Ribavirin and penciclovir: Ribavirin and penciclovir are guanosine analog, possess structural and functional similarities with those of favipiravir [25]. Though interaction of ribavirin with SARS-CoV-2 RdRp had been reported through molecular docking, they have not been found as a potent agent against SARS-CoV-2 [25].

Molnupiravir: Molnupiravir (MK-4482/EIDD-2801) showed optimistic outcomes against SARS-CoV-2 in human lung cells and on animals [26]. Compared to remdesivir, that is injected intravenously, molnupiravir can be ingested as a pill [26]. This criterion stands molnupiravir over others. However, recent data shows its no effect on hospitalized COVID-19 patients and its trial on non-hospitalized patients has been continuing.

Drugs used for some time but now withdrawn

Chloroquine and Hydroxychloroquine are the drugs that have been used for a short period during COVID-19 pandemic but now withdrawn due to lack of ameliorative effect on COVID-19 complication. Though FDA approved emergency use of these malarial drugs, later these had been withdrawn as these have not found effective against COVID-19. Rather, they cause serious side effects including cardiac complications [27].

Drugs in COVID-19 treatment pipeline

Amlodipine, nifedipine and losartan as well as ivermectin and famotidine have been studied in different countries to treat COVID-19 patients [28-30]. Oleandrin, a bio-component of the oleandrin shrub, had been reported with ameliorating effect on monkey kidney cells infected with SARS-CoV-2 [31]. Upto present time, there is lack of ample data providing positive outcome of these drugs against COVID-19.

Recombinant ACE-2

As SARS-CoV-2 uses the ACE2 receptor for entering into host cell, *Trojan horse stratagem* through tailor made ACE2 would aid in virus's endeavor futile [32]. On cell lines and animal models, recombinant ACE-2 proteins have shown promising outcomes [32].

Immune system mimicking strategy

Convalescent plasma

Plasma from the blood of the people who have recovered from COVID-19, is called convalescent plasma. Based on the idea that plasma loaded with antibodies against the SARS-CoV-2 might aid in halting Covid-19, the FDA granted emergency use authorization for convalescent plasma therapy [33]. Though some beneficial effects had been reported, one year's observation suggests that convalescent plasma therapy is not so much a curative agent for COVID-19 as was speculated [33].

Monoclonal antibodies

Monoclonal antibodies (mAb), derived from COVID-19 recovered people, have been thought promiscuous for the newly affected COVID-19 patients [34]. Preclinical studies on cells and animals showed COVID-19 ameliorating effect [34]. Monoclonal antibodies mostly undergone pre-clinical trials and emergency use authorization are bamlanivimab, etesevimab and REGN-COV2 (a cocktail of two mAbs - casirivimab and imdevimab) [34]. Negative sides of mAbs are that they must be provided through injection and would not be effective against new variants of SARS-CoV-2 as mAbs are derived from cloning of a single white blood cell type [34].

Cytokine inhibitors and other drugs

"Cytokine storm" is a grave concern of COVID-19 manifested by hyperinflammatory state [1,35]. Drugs used to lower cytokine storm include tocilizumab, baricitinib, fluvoxamine, leronlimab, lenzilumab and EXO-CD24. Besides, cytokine filtration, utilization of colchicine, anticoagulants and other antithrombotic drugs and antibiotic azithromycin, vitamin and mineral supplementation have been noted as COVID-19 therapeutics [35].

Vaccines used against sars-cov-2

A number of COVID-19 vaccines have been developed all over the world [36]. But all of them are not approved by the World Health Organization. Some of them are approved by the WHO for emergency usage [37]. Some of them are still in the clinical trials. However, the rate of effectiveness of all those vaccines is not same [38]. The side effects of all those vaccines also vary [39]. A vaccine must be safe for all. The WHO approved vaccines for emergency uses are messenger RNA based (Moderna and Pfizer/BioNtech), non-replicating viral vector-based (Astra Zeneca/University of Oxford, CanSino Biologics, Gamaleya Research Institute, Johnson & Johnson/Janssen), recombinant protein-based (Novavax and Medicagoerna) and inactivated virus based (Sputnik V of Russia, Sinovac of China and Serum Institute of India) Johnson and Johnson,oxford-astrageneca,sinopharm vaccine [40]. The Sputnik V of Russia is in the way to be approved by the WHO [41].

US Centers for Disease Control and Prevention (CDC) study finds that moderna and Pfizer vaccines are capable of preventing infections as well as symptoms of COVID-19.The study shows that a single of either Moderna or Pfizer provides 80% protection and vaccination with moderna or Pfizer vaccine decrease infections by 90% [42].

Vaccination helps to prevent hospital admission of people largely. An analysis of public health England showed that ,In case of people over 80, a single dose of Pfizer or oxford vaccine is around 80% effective after three or four weeks after the first dose [43]. On the other hand, people aged 70 or over, a single dose of Pfizer reduces the chance of death nearly 85% as the study of public health England suggested [44].

The Johnson and Johnson vaccine has also been found effective in the USA. Data released by Johnson and Johnson indicates that a single dose of this vaccine is 66% effective in preventing moderate to severe COVID-19 and 100% effective in preventing COVID-19–related hospitalization and death [45]. The level of protection against moderate to severe SARS-CoV-2 infection was 72% in the US, 66% in Latin America, and 57% in South Africa, and nearly all cases of SARS-CoV-2 (95%) in South Africa were caused by infection with a SARS-CoV-2 variant from the B.1.351 lineage [45].

The Oxford-Astrazeneca vaccine trial was carried out in the UK and the data suggest that it provides protection against the original pandemic virus .The data from trials also suggest that it also protects from the novel variant, B.1.1.7 [46]. The Astrazeneca trial in south Africa suggested that a two dose of this vaccine provides minimal protection against mild–moderate

SARS-CoV-2 infection from the B.1.351 coronavirus variant [46].

The China's Sinophram company demanded that its COVID-19 vaccine is 79.34% effective [48]. An interim analysis of a human trial of this vaccine took place in the United Arab Emirates [48]. The vaccine is 86% effective as said by the United Arab Emirates health ministry and 100% effective in preventing moderate and severe cases of the disease [48]. The WHO's Strategic Advisory Group of Experts on Immunization (SAGE) suggested that this Vaccine's efficacy for symptomatic and hospitalized disease was estimated to be 79%, all age groups combined [48]. On the basis of all available evidence, WHO recommends the vaccine for adults 18 years and older, in a two-dose schedule with a spacing of three to four weeks [48].

The Sinovac vaccine is another vaccine made by the China and expected to be approved by the WHO very soon [48]. The Turkish officials stated that sinovac vaccine has the efficacy rate of 91.25% after a small clinical trial. Brazil's officials stated that the vaccine has a efficacy over 50 percent [48]. The Indonesian food and drug monitoring agency found this vaccine's efficacy 65.3% after a local clinical trial [48].

Russia developed a vaccine named Sputnik V which got approval in Russsia to use [49]. WHO is also analyzing its data to approve it for emergency usage [49,50]. The Gamaleya National Research Center of Epidemiology and Microbiology and the Russian Direct Investment Fund (RDIF) have suggested that the Sputnik V Covid-19 vaccine has 97.6% efficacy [49,50].

Conclusion

Although different therapeutic strategies have been applied against SARS-CoV-2 to tackle COVID-19, none of them have been proven to be 100% effective. Already available medication could only alleviate some symptoms. Thus, the global humanity is in dire need of any single or multiple therapeutic approaches that could withstand COVID-19. We remain hopeful of future research and development in drug and vaccination programs so that the entire humanity remain safe.

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